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Oxidative stress as a mediator of the effect of air pollution on respiratory disease

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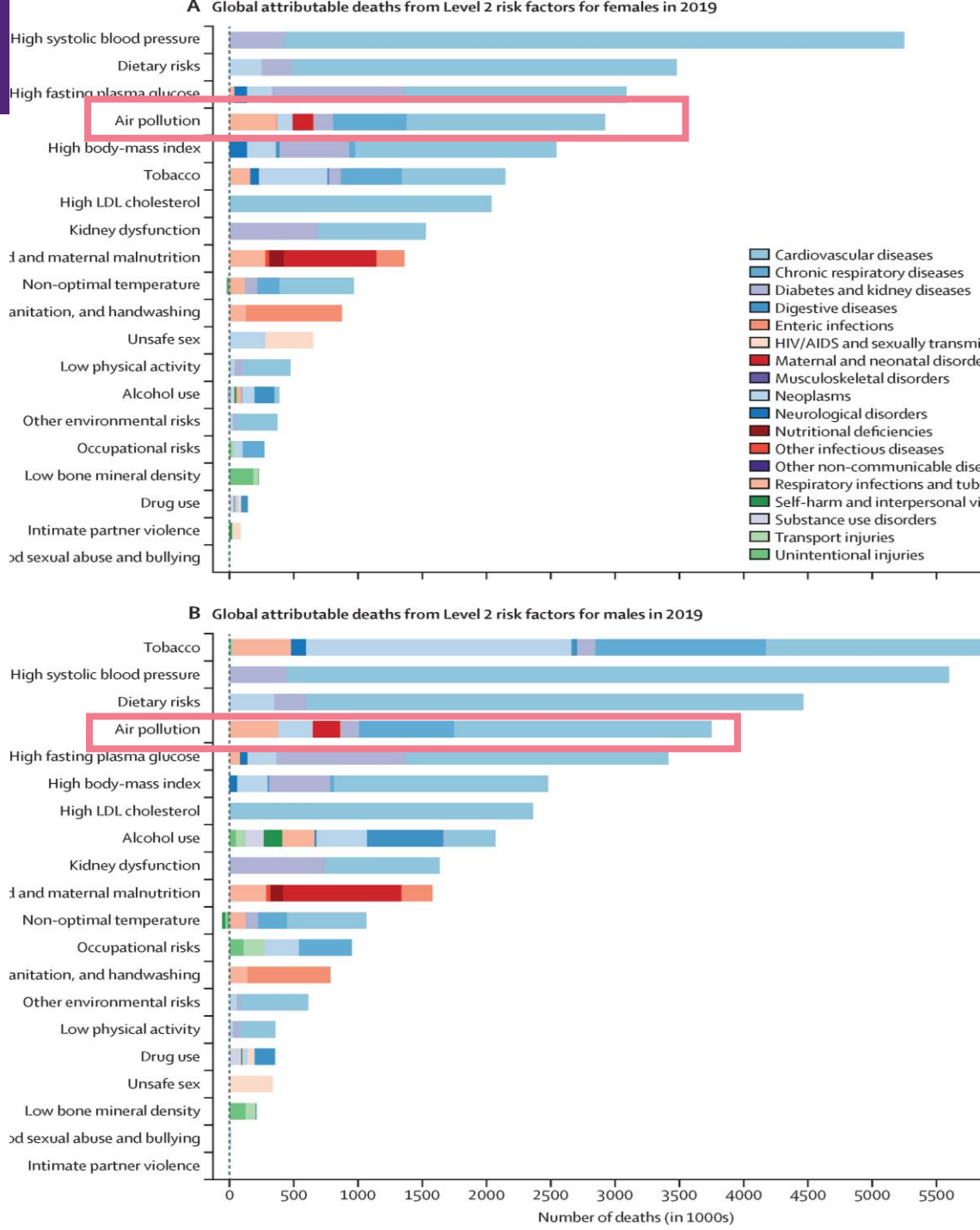
Air pollution and respiratory disease

Well accepted that poor air quality is associated with respiratory conditions

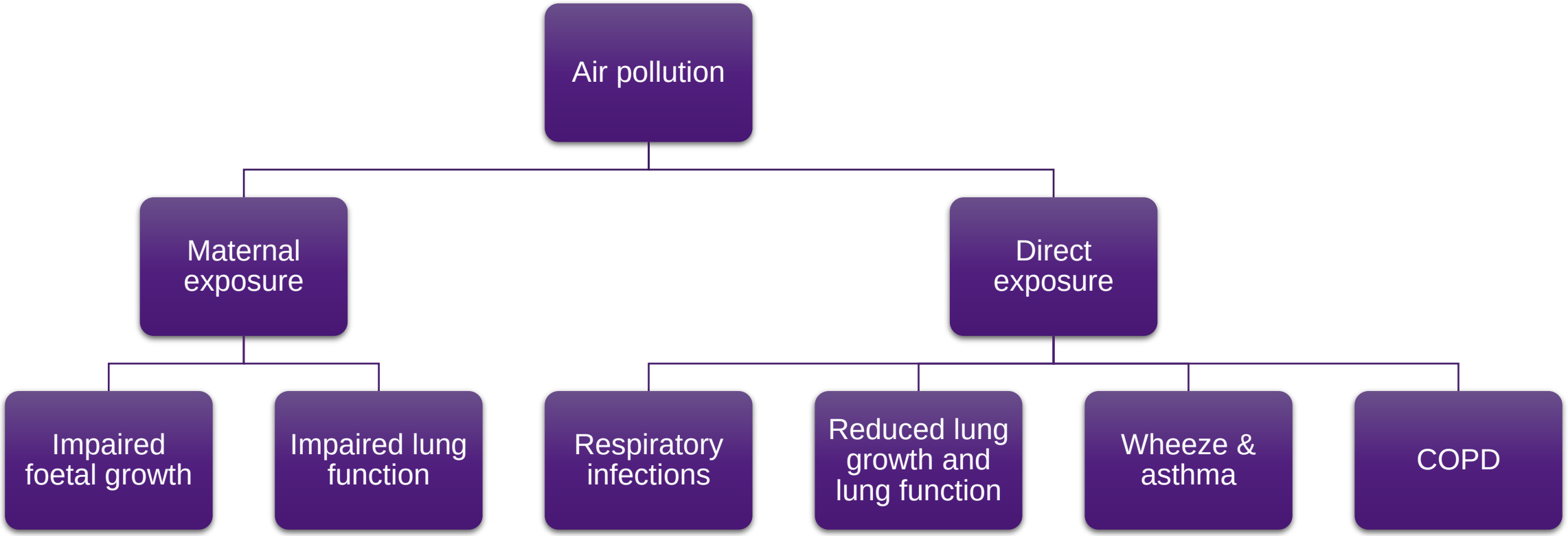
Lancet Commission on Pollution and Health found that 6.5 million deaths in 2015 were attributable to air pollution

Air quality predicted to get worse under climate change



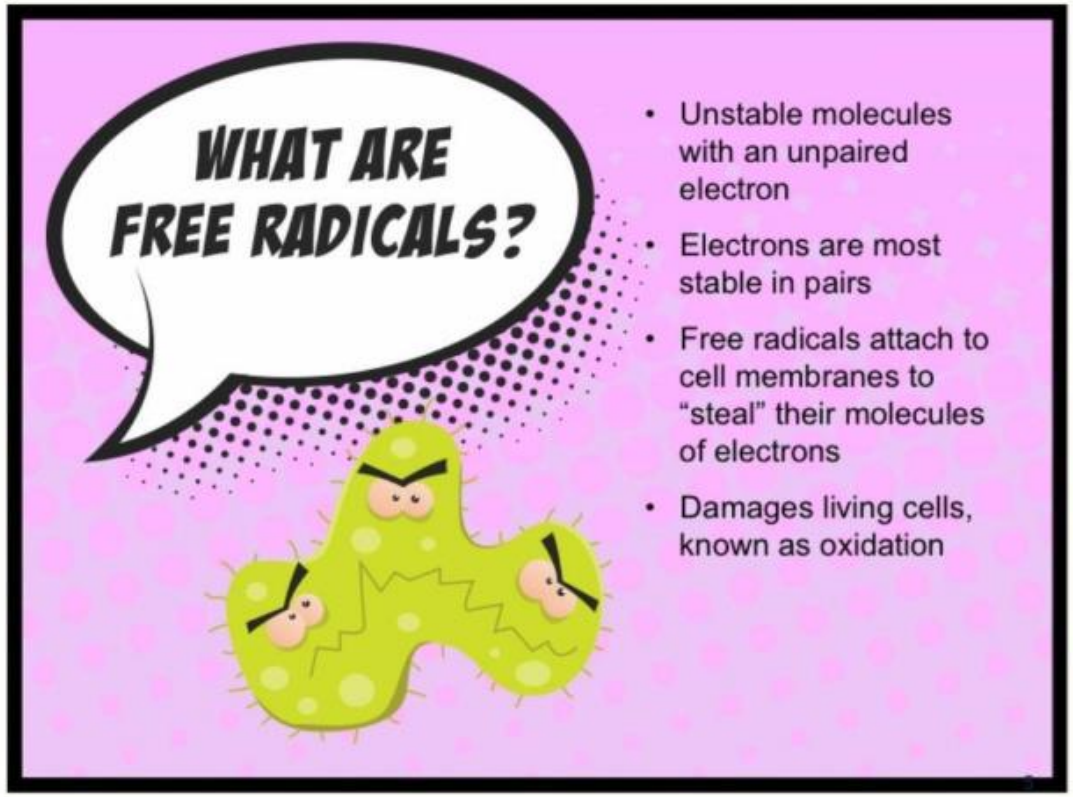
(Landrigan et al., 2018; Murray et al., 2020)

Respiratory effects



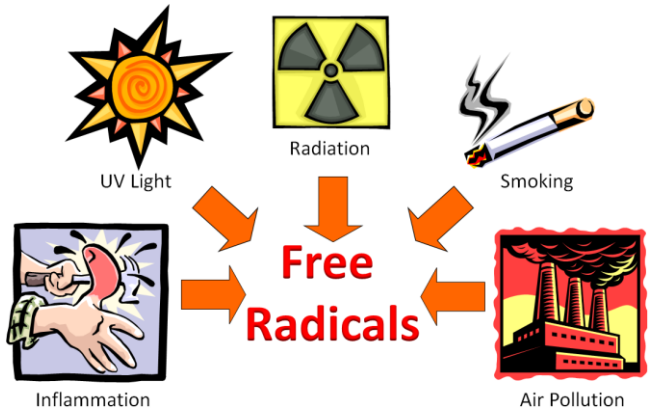
(Boeyen et al., 2017; Gasana et al., 2012; Goldizen et al., 2015; Hansen et al., 2008; Hehua et al., 2017; Latzin et al., 2009; Schultz et al., 2012; Stern et al., 2013)

Free radicals



Four major sources of free radicals: endogenously generated from biochemical processes, produced by neutrophils, produced after radiation exposure, environmental sources.

The removal of an electron by a free radical can set off chain reactions of free radicals in the tissues and lead to tissue damage.



(Pizzino et al., 2017)

Oxidative stress

The body has complex defences against free radicals

- Enzymes such as dismutase and peroxidase
- Antioxidants
- Metal binding proteins

Oxidative stress can be defined as a state where production/exposure of free radicals is greater than the antioxidant defences.

(Betteridge, 2000)

Air pollution and oxidative stress

There are various mechanisms through which air pollutants can induce oxidative stress:

- Oxidant activity (ozone)
- Directly free radical (nitrogen dioxide)
- Redox catalysts (components in particles such as Fe, Cu, Ni, quinones)
- Internally metabolised to reactive electrophiles (PAHs)
- Introduction of metals in the lung
- Trigger inflammation pathways
- Inactivate phosphatases
- Interfere with mitochondrial function

(Mudway et al., 2020)

Environmentally persistent free radicals

Particulate matter has given rise to a newly discovered form of free radical – EPFRs

- Produced through the binding of organic pollutants to the surface of particles.
- The organic pollutant reduces the metal and resulting OH- loss forms a stable free radical

EPFRs participate in the redox cycle in biological systems and produce ROS.

Multiple mechanisms through which affect health: induction of oxidative stress, lipid peroxidation, lysosomal membrane permeabilization; autophagy; and induction of cell death by apoptosis or necrosis

EPFRs induced asthma in animal models via a mechanism involving neutrophils and Th17 cells

(Lee et al., 2014; Stephenson et al., 2016)

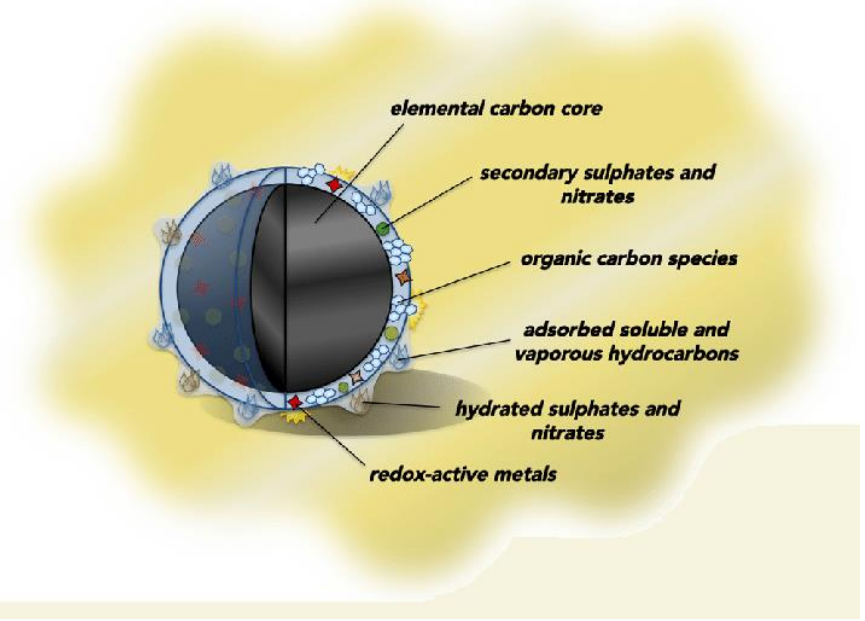
Air pollution, oxidative stress & the lung

Exposure to air pollution causes oxidative stress in the lung

- Both ozone and NO_2 likely exert their effects through secondary mechanism – where their presence triggers a cascade that starts free radical processes. Both pollutants interact with lung lining fluid and not directly with the cells.
- Triggers inflammatory cells to migrate to the lung -> release free radicals and cause tissue damage in absence of infectious agents

Increasing evidence that metals adsorbed to surface of PM likely associated with adverse health outcomes through induction of oxidative stress.

Antioxidant defences in the lung should protect against air pollution, however if these defences are overcome or an individual has a lower antioxidant capacity then harm may occur.



(Kelly, 2003)

Air pollution and oxidative stress

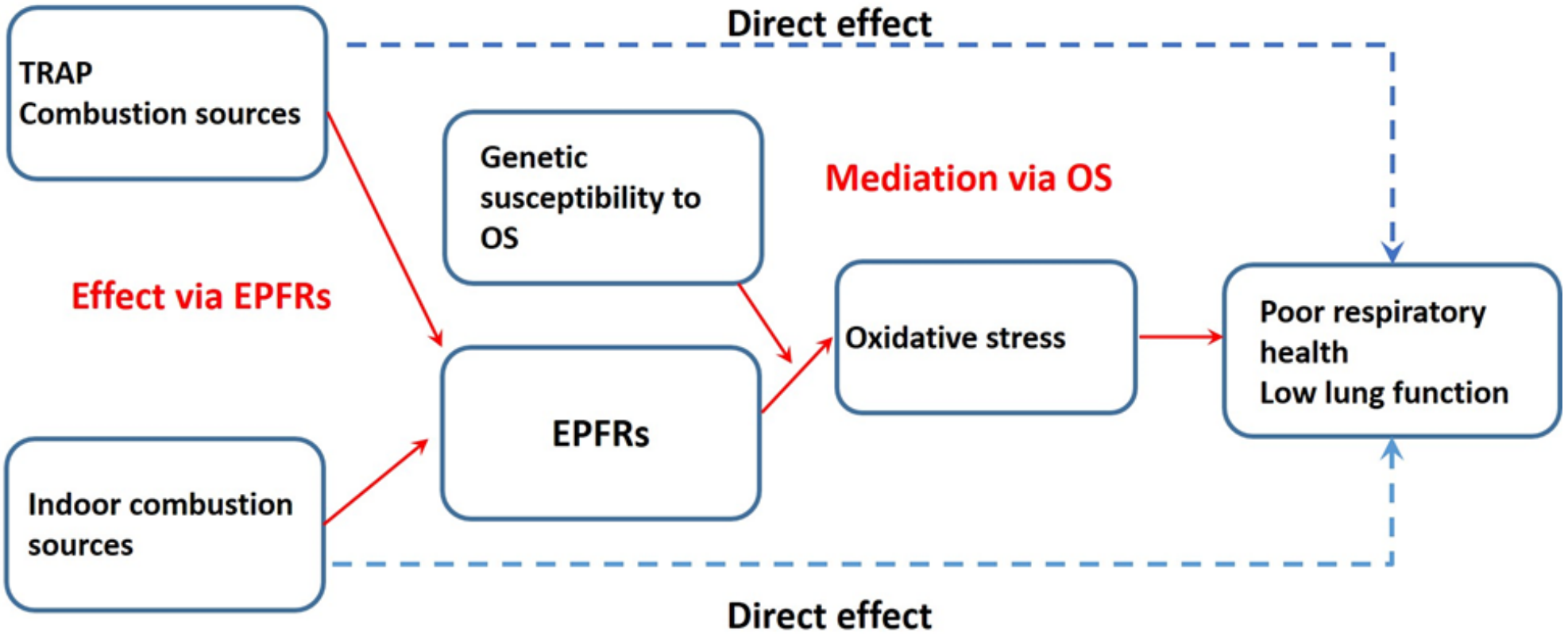
Study of air quality, pre-, during and post-Beijing Olympics found that both urinary and expired breath condensate malondialdehyde (MDA) decreased during the period of the air quality improvements for the Olympics.

Children exposed to high levels of TRAP in Mexico City had increased levels of MDA in exhaled breath condensates. Subjects with “null” or reduced function mutations in anti-oxidant defence genes, such as GSTP1, showed increased susceptibility to TRAP exposure, and asthma was more likely in children with TRAP exposure if they showed increased expression of the redox-sensitive transcription factor, NFE2L2 (NRF2) gene.

Does genetic risk of oxidative stress predispose to greater harm from air pollution?

(Gong et al., 2013; MacIntyre et al., 2014; Romieu et al., 2008; Ungvari et al., 2012)

Oxidative stress as a mediator



Current work

Studies to date have not integrated across outdoor and indoor air pollutants or measured indoor EPFR levels as a likely mediating factor.

Our current study seeks to understand the role of oxidative stress in the relationship between air pollution and lung outcomes.

Two major aims:

1. Identify the determinants EPFR in house dust
2. To understand the role of EPFR-induced oxidative stress (OS) on child respiratory outcomes (lung function, respiratory infections, asthma) at age 4 years

Thank you

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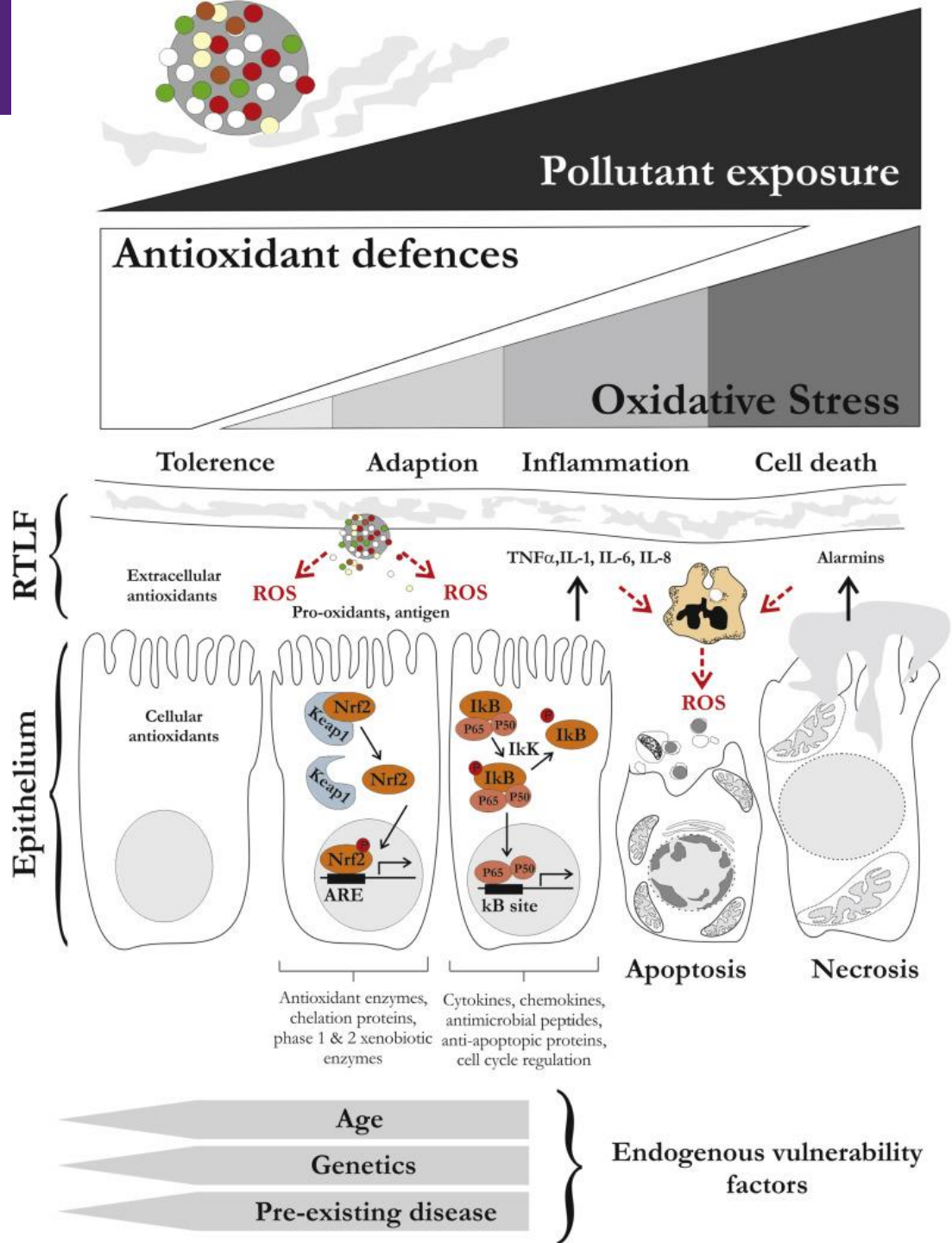
Pollutant exposure
Antioxidant defences
Oxidative Stress
Tolerence
Adaption
Inflammation
Cell death
RTLF
Epithelium
Extracellular antioxidants
ROS
ROS
Pro-oxidants, antigen
TNFα,IL-1, IL-6, IL-8
Alarmins
Cellular antioxidants
Nrf2
Keap1
Keap1
Nrf2
Nrf2
ARE
IkB
P65
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IkB
IkB
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P50
P65
P50
kB site
ROS
Apoptosis
Necrosis
Antioxidant enzymes, chelation proteins, phase 1 & 2 xenobiotic enzymes
Cytokines, chemokines, antimicrobial peptides, anti-apoptopic proteins, cell cycle regulation
Age
Genetics
Pre-existing disease
Endogenous vulnerability factors

EPFR formation

- An organic pollutant forms a weak bond with a metal on the surface of a particle (physisorption);
- water or hydrogen halide (HX) is released in the combustion process to form a strong bond with the metal (chemisorption) [12];
- the organic pollutant reduces the metal by taking an electron, resulting in the formation of the radical;
- OH^- is released forming a stable EPFR (figure 1).

Figure 1: Process of EPFR formation